WE CLAIM:

1. A method for identifying a cellular component to which a small molecule is capable of binding, comprising:

(a) providing a hybrid ligand consisting essentially of two ligands, identified as ligand A and ligand B that are linked together, wherein ligand A has a specificity for a predetermined target and forms an irreversible (covalent) bond; and ligand B is the small molecule:

(b) introducing the hybrid molecule into at least one sample, the sample containing an environment, the environment containing;

(i) a first expression vector, including DNA encoding the target for ligand A, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector including a random DNA fragment encoding a polypeptide linked to a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second hybrid proteins;

(c) permitting the hybrid molecule to bind covalently the first hybrid protein through ligand A and the second hybrid protein through ligand B so as to activate the expression of the reporter gene;

(d) identifying those samples expressing the reporter gene; and

(e) characterizing the second hybrid protein in the samples identified in (d) so as to determine the cellular component to which the small molecule has a binding affinity.

2. A method according to claim 1, wherein the environment in step (b) is a cell lysate.

3. A method according to claim 1, wherein the environment in step (b) is a population of cells or a single cell.

4. A method according to claim 3, wherein the cells are genetically altered.

Duplicate (4) A method according to claim 3, wherein the cells are genetically altered.

5. A method according to claim 3, wherein the cells are eukaryotic cell.

SUB D3 6. A method according to claim 1, wherein the environment in step (b)is selected from a group consisting of insect cells, yeast cells, mammalian cell, and their lysates.

7. A method according to claim 5, wherein the cells are yeast cells.

8. A method according to claim 5, wherein the cells are mammalian cells.

9. A method according to claim 7, further comprising the step of enhancing the permeability of the yeast membrane.

10. A method according to claim 9, wherein the step of enhancing the permeability of the yeast membrane further comprises selecting yeast mutants (*e.g.*, pdr5 and snq2) having enhanced membrane permeability.

11. A method according to claim 3, further comprising introducing the hybrid molecule into the cells by electroporation.

SUB D3 12. A method according to claim 1, wherein the first and second transcription module of step (b)(i) and (b)(ii) is selected from the group consisting of a DNA binding protein and a transcriptional activator.

SUB D4 13. A method according to claim 1, wherein the second expression vector of step (b)(ii) contains a random DNA fragment of a size suited for encoding a gene product wherein the DNA fragment is from a library of DNA.

14. A method according to claim 13, wherein the DNA fragments in the library are selected from the group consisting of genomic DNA, cDNA and synthetic DNA.

SUB D3 15. A method according to claim 1, wherein the DNA fragment of step (b)(ii) is obtained from a plurality of libraries.

16. A method according to claim 14, wherein the cDNA library is derived from an immune cell.

17. A method according to claim 16, wherein the cDNA is derived from an immune cell capable of producing an immune response to the small molecule contaminant.

18. A method according to claim 1, wherein the ligand A or B of step (a) is a mechanism based irreversible enzyme inactivator (*e.g.*, aspirin-cyclooxygenase).

19. A method according to claim 1, wherein the small molecule has a known biological function.

20. A method according to claim 1, wherein the small molecule is obtained from a combinatorial library.

21. A method according to claim 20, wherein the small molecule is obtained from a combinatorial library of nucleic acids.

22. A method according to claim 20, wherein the small molecule is obtained from a combinatorial library of polypeptides.

23. A method according to claim 20, wherein the small molecule is obtained from a combinatorial library of small organic molecules.

24. A method according to claim 1, wherein the small molecule is an environmental contaminant.

25. A method according to claim 1, wherein the reporter gene is selected from the group consisting of Lac Z, GFP, luciferase, Ura 3, His 3, Leu2 and an antibody coding region.

26. A method according to claim 1, wherein the cell component is a protein.

27. A method according to claim 24, wherein the steps (b) - (e) of the method are repeated using an expression vector encoding the second hybrid protein of step (e) and a hybrid molecule containing ligand A and ligand B. in the presence of a preparation of random small molecules for competitive binding with the hybrid molecule and identifying the small molecule capable of competitively binding the target molecule for searching for new target molecules in an iterative process.

28. A method for identifying a small molecule capable of binding a molecular target, comprising:

(a) providing a preparation of a library of hybrid molecules wherein each hybrid molecule consists essentially of two ligands, identified as ligand A and ligand B that are covalently linked, wherein ligand A has a specificity for a first predetermined target and ligand B is a random small molecule;

(b) introducing the preparation into at least one sample, the samples containing an environment, the environment containing;

(i) a first expression vector, including a DNA encoding the first target, linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector including DNA encoding the molecular target, linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein; and

(iii) a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the lest and second target protein;

(c) permitting the hybrid molecule to bind to the first hybrid protein and the second hybrid protein so as to activate the expression of the reporter gene:

(d) identifying those samples expressing the reporter gene; and

(e) characterizing ligand B so as to identify the small molecule capable of binding the molecular target.

29. A method for identifying a small molecule capable of competitively binding a molecular target in the presence of a known binding ligand, comprising:

(a) providing a hybrid molecule consisting essentially of two ligands identified as ligand A and ligand B that are covalently linked, wherein ligand A has a specificity for a first predetermined target and ligand B has a specificity for a second predetermined target;

(b) introducing the hybrid molecules into at least one sample, the samples containing an environment, the environment containing;

(i) a first expression vector, including a DNA fragment encoding the first target. linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(ii) a second expression vector including DNA encoding the second target. linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein;

(iii) a third vector including a reporter gene wherein the expression of the reporter gene is conditioned on the proximity of the first and second target; and

(iv) at least one random small molecule identified as ligand C;

(c) permitting the hybrid molecule to bind to the first hybrid protein and the second target so as to activate the reporter gene in the presence of ligand C;

(d) identifying the samples distinguished by the absence of expression of the reporter gene; and

(e) characterizing ligand C so as to determine the small molecule capable of binding competitively to the molecular target;

30. A method according to claim 29, wherein the molecular target is the second target protein of claim 1.

31. A kit for detecting interactions between pharmacologically relevant small molecules and proteins comprising;

(a) a preactivated ligand A and reagents for forming a hybrid molecule with at least one type of ligand B;

(b) a first expression vector including DNA encoding the binding protein for Ligand A linked to a coding sequence for a first transcriptional module for expression as a first hybrid protein;

(c) a second expression vector including a random DNA fragment encoding a polypeptide linked to a coding sequence for a second transcriptional module for expression as a second hybrid protein;

(d) a third vector including a reporter gene wherein transcription of the reporter gene is conditioned on the proximity of the first and second target proteins;

(e) an environment for transcription and translation of the hybrid proteins and reporter genes; and

(f) a means for detecting the expression of the reporter gene following the formation of a trimeric complex between the hybrid ligand and the hybrid proteins.